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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/315,292	05/20/1999	CLARENCE FRANK BENNETT	ISIS-3561	6344

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EXAMINER	
BOWMAN, AMY HUDSON	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/315,292	BENNETT ET AL.	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *66-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *66-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/22/03, 12/17/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 2/15/2006 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 11/15/2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 66-75 are pending in the application.

Response to Arguments-35 U.S.C. 102

Claims 66 and 72-74 stand rejected under 35 U.S.C. 102(b) as being anticipated by Kole et al. (US 5,627,274), for the reasons of record set forth in the office action mailed 6/14/05 and maintained 11/15/2005.

Applicant argues that the current amendment to claim 66 to recite that the particle size is about 1 to about 5 microns should obviate the instant rejection because Kole et al. provide no teaching regarding particle size for delivery to the lung.

Contrary to applicant's argument, Kole et al. teach a method of administering an oligonucleotide into a lung of a patient as a therapeutic in the treatment of disease, such as cystic fibrosis, via administering an aerosolized formulation of respirable particles to the lungs (see columns 5 and 6).

As evidenced by Clark (Aerosol Science and Technology, 22, 1995, pages 374-391), the respirable particles of Kole et al. would necessarily be about 1 to about 5 microns, as instantly recited.

Clark teaches that the successful administration of compounds to the lung requires the generation and delivery of 'fine' aerosols. Clark teaches that in order to avoid inertial impaction in the oropharyngeal cavity and reach the lung, aerosol particles of 7 μm or less are required. Clark teaches that to reach the peripheral lung, the site of absorption for systemic therapy, particles of the order of 2 to 3 μm are required. Clark teaches that one of the major requirements of any medical inhaler is that it generates aerosols containing particles within the "respirable" size range (see page 374).

Therefore, the "respirable" particles of Kole et al. would necessarily be in the "respirable" size range, as evidenced by Clark.

This is further evidenced by Nyce et al. (WO/96/40266). Nyce et al. teach that particles comprised of antisense compound should be of respirable size, that is particles of a size sufficiently small to pass through the mouth and larynx upon inhalation and into the bronchi and alveoli of the lungs. Nyce et al. teach that in general, particles ranging from about .5 to 10 microns in size are respirable (see page 10).

Additionally, applicant asserts that Kole does not address cell uptake because the assays are not performed in cells. As explained in the office action mailed 11/15/2005, Kole et al. do not need to specifically exemplify the teachings in order for the teachings to be enabled. Kole et al. teach each of the method steps instantly claimed and therefore are as enabled as the instant claims. Furthermore, the elements

of Kole et al. are instantly claimed, which are presumed to be enabled. Since Kole et al. specifically teach a method of administering an oligonucleotide into a lung of a patient as a therapeutic in the treatment of disease via administering an aerosolized formulation of respirable particles to the lungs, the oligonucleotides of Kole et al. would necessarily be taken up by a cell in the lung. As evidenced by the 1.132 declaration submitted by applicant, these same method steps result in oligonucleotide uptake to at least one cell type in the lung.

Therefore, the instant invention is anticipated by Kole et al.

New Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 66 and 72-75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kole et al. (US 5,627,274), as evidenced by Clark (Aerosol Science and Technology, 22, 1995, pages 374-391) and Nyce et al. (WO 96/40266), as explained in the 35 U.S.C. 102(b) rejection above, in view of Nyce et al. (WO 96/40266).

The invention of the above claims is drawn to a method of administering an oligonucleotide into the lung of a mammal, comprising aerosolizing the oligonucleotide wherein the aerosol particles have a size of about 1 to about 5 microns, and introducing

the aerosolized oligonucleotide into the lung of the mammal, wherein the sugar moiety of at least one nucleoside unit is a 2'-O-substitued nucleoside unit, and the oligonucleotide is taken up by at least one cell type in the lung. The oligonucleotide is in an aqueous media such as sterilized, pyrogen free water or saline solution or in a saline solution or a powder.

Kole et al. teach a method of administering an antisense oligonucleotide into a lung of a patient as a therapeutic in the treatment of disease, such as cystic fibrosis, via administering an aerosolized formulation of respirable particles to the lungs (see columns 5 and 6). Kole et al. teach formulations comprising the antisense oligonucleotide comprising sterile aqueous and non-aqueous solutions of the active compound, including saline or water. Kole et al. teach 2'-O-methyl modified oligonucleotides and teach that these modified oligonucleotides are resistant to nucleases and from stable hybrids with RNA that are not degraded by RNase H (see column 8).

Kole et al. do not need to specifically exemplify these teachings in order for the teachings to be enabled. Kole et al. teach each of the method steps instantly claimed and therefore are as enabled as the instant claims. Furthermore, the elements of Kole et al. are instantly claimed, which are presumed to be enabled. Since Kole et al. specifically teach a method of administering an oligonucleotide into a lung of a patient as a therapeutic in the treatment of disease via administering an aerosolized formulation of respirable particles to the lungs, the oligonucleotides of Kole et al. would necessarily be taken up by a cell in the lung. As evidenced by the 1.132 declaration submitted by

applicant, these same method steps result in oligonucleotide uptake to at least one cell type in the lung.

Kole et al. do not teach oligonucleotides formulated in powders.

Nyce et al. teach that respirable antisense oligonucleotides can be formulated to be liquid or solid (see page 10). Liquid compositions comprise the antisense compound and sterile, pyrogen free water. Nyce et al. teach that suitable formulations for delivery include powders (see page 12). Nyce et al. teach that respirable antisense oligonucleotides can be formulated into powders and effectively delivered with a metered dose inhaler.

It would have been obvious to one of ordinary skill in the art to formulate the antisense oligonucleotide taught by Kole et al. in a powder, as taught by Nyce et al.

One would have been motivated to formulate the respirable antisense oligonucleotide of Kole et al. in a powder because Nyce et al. teach that respirable antisense oligonucleotides are formulated into powders to be effectively delivered in a metered dose.

Finally, one would have a reasonable expectation of success to formulate the respirable antisense oligonucleotide of Kole et al. in a powder because powders were known to be successful formulations for respirable antisense oligonucleotides, which are easily formulated into powders, rendering them useful for delivery via metered dose inhalers of various designs, as taught by Nyce et al.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention

was made.

Claims 66-75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kole et al. (US 5,627,274), in view of Nyce et al. (WO 96/40266), as explained in the 35 U.S.C. 103(a) rejection above, further in view of Nicklin et al. (WO 98/09633).

The invention of the above claims is drawn to a method of administering an oligonucleotide into the lung of a mammal, comprising aerosolizing the oligonucleotide wherein the aerosol particles have a size of about 1 to about 5 microns, and introducing the aerosolized oligonucleotide into the lung of the mammal, wherein the sugar moiety of at least one nucleoside unit is a 2'-O-substitued nucleoside unit, and the oligonucleotide is taken up by at least one cell type in the lung. The invention is further drawn to modifications of the oligonucleotide. The oligonucleotide is in an aqueous media such as sterilized, pyrogen free water or saline solution or in a saline solution or a powder.

Kole et al. does not teach 2'-alkoxyalkoxy, 2'-O-methoxyethyl, or 2'-O-dialkylaminooxyalkyl modifications. Kole et al. does not teach phosphorothioate, methylphosphonate, or non-phosphorous containing linkages.

Nyce et al. is further relied upon for teaching methylphosphonate and phosphorothioate linkages to render respirable antisense oligonucleotides more stable *in vivo* (see page 7).

Nicklin et al. teach antisense oligonucleotides and teach that modification of antisense oligonucleotides confers increased nuclease resistance, increased uptake

into cells, and increased binding affinity for the RNA target (see page 2). Nicklin et al. teach 2' modifications including 2'-alkoxyalkoxy, 2'-O-methoxyethyl, and 2'-O-dialkylaminooxyalkyl modifications. Nicklin et al. teach phosphorothioate, methylphosphonate, and non-phosphorous containing linkage modifications (see pages 4 and 5).

It would have been obvious to one of ordinary skill in the art to incorporate 2'-alkoxyalkoxy, 2'-O-methoxyethyl, or 2'-O-dialkylaminooxyalkyl modifications, as taught by Nicklin et al., as well as phosphorothioate or methylphosphonate linkages, as taught by Nyce et al. and Nicklin et al. into the antisense oligonucleotide of Kole et al. It would have been obvious to incorporate non-phosphorous containing linkage modifications, as taught by Nicklin et al. into the antisense oligonucleotide of Kole et al.

One would have been motivated to incorporate each of the modifications into the antisense oligonucleotides of Kole et al. because Nicklin et al. teach that these modifications confer increased nuclease resistance, increased uptake into cells, and increased binding affinity for antisense oligonucleotides. Additionally, Nyce et al. teach that modifications render respirable oligonucleotides more stable *in vivo*. Furthermore, Kole et al. teaches 2'-O-methyl modified oligonucleotides and teach that these modified oligonucleotides are resistant to nucleases and from stable hybrids with RNA that are not degraded by RNase H (see column 8), so one would have been motivated to incorporate other modifications that were known to offer the same benefits.

One would have a reasonable expectation of success to incorporate each of the modifications taught by Nicklin et al. or Nyce et al. into the antisense oligonucleotides of

Kole et al. because each of these modifications were known to benefit antisense oligonucleotides, as taught by Nicklin et al. or Nyce et al. Therefore, one would reasonably expect for these modifications to increase nuclease resistance, increase uptake into cells, and increase binding affinity of the oligonucleotides of Kole et al. as well.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is 571-272-0755.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Amy H. Bowman
Examiner
Art Unit 1635

JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER